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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/982,968	10/22/2001	Charles B. Grissom	2317-107	8772

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EXAMINER	
ZARA, JANE J	

ART UNIT	PAPER NUMBER
1635	5

DATE MAILED: 06/27/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/982,968	Grissom et al
Examiner	**Art Unit**
Jane Zara	1635

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Oct 22, 2001* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-43* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-43* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☒ The drawing(s) filed on *Oct 22, 2001* is/are a) ☒ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *3, 4*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Claims 1-43 are pending in the instant application.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 40 and 41 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 40, line 3, "the substituents" lacks proper antecedent basis.

In claim 41, line 1, "said targeting molecule" lacks proper antecedent basis.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-43 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to methods of administering any bioactive agent to cells or tissues in vitro or in vivo comprising the administration of the bioactive agent covalently conjugated to a cobalt atom in an organocobalt complex, through any non-reactive atom in the bioactive agent molecule, wherein the bioconjugated bioactive agent is targeted to the cell or tissue site in an inactive form and activated upon cleavage from the organocobalt complex.

The specification and claims do not describe elements that are essential the genus comprising a covalent conjugated non-reactive atom in the bioactive agent molecule, whereby it is covalently conjugated to the cobalt atom of the organocobalt complex, nor of the genus comprising an inactive form of a bioactive agent that is cleaved to an active form. The specification and claims do not indicate what distinguishing attributes are concisely shared by the members of the genera comprising inactive/active forms of bioactive agents, nor of covalently conjugated cobalt atoms and bioactive agent molecules in any and/or all organocobalt complexes. The disclosure does not clarify what common attributes are encompassed by such covalent conjugates and such inactive/inactive forms of bioactive agents. Thus, the scope of the claims includes numerous structural variants and the genera are highly variant a significant number of structural differences between members of a given genus is permitted. Concise structural features that could distinguish structures or compounds within a genus from others are missing from the disclosure. No common structural attributes identify the members of the genus comprising covalent cobalt atom-bioactive agent molecules involving a non-reactive atom in the bioactive agent, and no common structural attributes identify the members of the genus comprising

inactive/active bioactive molecules, whereby conversion from inactive to active biological agents occurs upon cleavage. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general guidance is what is needed. The specification fails to teach or adequately describe a representative number of species in each genera such that the common attributes or characteristics concisely identifying members of each proposed genera are exemplified and because each genus is highly variant, the description provided in insufficient. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the various genera claimed. Thus, Applicant was not in possession of the claimed genera.

Claims 1-43 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the in vitro delivery, sonolysis and photolysis of B_{12} and Co[SALEN] bioconjugates to target cells, does not reasonably provide enablement for the targeting of any and/or all cells and tissue sites in vivo, and the subsequent cleavage via cellular displacement, metabolic enzymatic cleavage, sonolysis, photolysis or cleavage of an inactive bioactive agent, thereby rendering it active within the target cells or tissues. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are drawn to methods of administering any bioactive agent to cells or tissues in vitro or in vivo comprising the administration of the bioactive agent covalently conjugated to a cobalt atom in an organocobalt complex, through any non-reactive atom in the bioactive agent

molecule, wherein the bioconjugated bioactive agent is targeted to the cell or tissue site in an inactive form and activated upon cleavage from the organocobalt complex.

The following factors have been considered in determining that the specification does not enable the skilled artisan to make and/or use the invention over the scope claimed.

The state of the prior art and the predictability or unpredictability of the art. The following references are cited herein to illustrate the state of the art of target cell or tissue delivery and metabolism of organocobalt delivery devices. The high level of unpredictability regarding the successful targeting, delivery and appropriate metabolism of organocobalt complexes has been illustrated in the teachings of Quadros et al, Collins et al and McEwan et al. Quadros et al, for example, teach that the intracellular events leading to the disposition of various cobalt forms are largely unknown (See last paragraph on p. 395-top paragraph on p. 396). Quadro et al found that the efflux of cobalt and cobalt complexes from target cells was not predictable and stated the question: "Whether the efflux phenomenon is a peculiarity of L-1210 cells in culture or a normal function of cells both in vivo and in vitro needs to be determined." (Page 401, last full paragraph). In addition, a biodistribution study involving cobalamin in cancer patients led to the conclusion that "Further evaluation of cobalamin analogs and their interaction with transport proteins and cellular receptors within malignant tissue and infection is warranted.") (See Collins et al, abstract on p. 568). Collins et al found enhanced cellular uptake to occur in some malignant tissues, but not others (See e.g. p. 571, second and fourth full paragraphs on the right; p. 572, second full paragraph; p. 573, last full paragraph). Furthermore, McEwan et al have shown various factors

that contribute to the unpredictability of cobalt delivery devices, including the photolability of the derivatized cobalt metal center in vitamin B12 (p. 1131, second full paragraph of the introduction), and varying binding affinities for transcobalamin II, depending on the nature of derivatization of the cobalt delivery device (p. 1131, last full paragraph).

The amount of direction or guidance presented in the specification AND the presence or absence of working examples. Applicants have not provided guidance in the specification toward a method of delivering bioactive agents to target cells or tissues sites in vivo comprising the administration of bioconjugates comprising covalent linkage between a non-reactive atom of a bioactive agent and the cobalt atom of any and/or all organocobalt complexes, and further whereby cleavage occurs by either cellular displacement, cellular B_{12} metabolic enzymes or external signals, rendering the bioactive agent active from an inactive, conjugated form. The specification teaches the uptake of B_{12} and Co[SALEN] bioconjugates in various target cells in vitro, as well as teaching the sonolysis of these bioconjugates in vitro. The specification also teaches the increased activity of chlorambucil in target cells in vitro following its delivery as a cobalamine bioconjugate. One skilled in the art would not accept on its face the examples given in the specification of the in vitro delivery of B_{12} and co[SALEN] bioconjugates as being representative or correlative of the in vivo delivery of any and/or all bioactive agents covalently conjugated to a cobalt atom in any and/or all organocobalt complexes, through a non-reactive atom in the bioactive agent molecule, and further whereby the bioactive agent is delivered to the appropriate target cell or tissue in an inactive, bioconjugated form and is lysed via cellular

displacement, B12 metabolic enzymes or external signals and upon lysis is converted to an active bioactive agent, in view of the lack of guidance in the specification and known unpredictability associated with the successful delivery and subsequent cellular metabolism of organocobalt complexes as delivery devices for bioactive agents in vivo. One skilled in the art would not accept on its face the examples given in the specification of in vitro cellular delivery and lysis of chlorambucil cobalamin bioconjugates as being representative or correlative of the ability to predictably deliver any inactive bioactive agent covalently linked to a cobalt atom in an organocobalt delivery device to any cell or tissue in vivo and further whereby the bioactive compound is converted from an inactive to an active form once delivered to the target cell or tissue. The specification as filed fails to provide particular guidance which resolves the known unpredictability in the art associated with the delivery of inactive biological agents covalently linked to the cobalt atom of the organocobalt complex, and further whereby the bioactive agent is rendered active upon cleavage from the organocobalt complex.

The breadth of the claims and the quantity of experimentation required. The claims are drawn to methods of administering any bioactive agent to cells or tissues in vitro or in vivo comprising the administration of the bioactive agent covalently conjugated to a cobalt atom in an organocobalt complex, through any non-reactive atom in the bioactive agent molecule, wherein the bioconjugated bioactive agent is targeted to the cell or tissue site in an inactive form and activated upon cleavage from the organocobalt complex. The quantity of experimentation required to practice the invention as claimed would require the *de novo* determination of

accessible target sites and formulations to target appropriate cells and /or tissues, whereby the organocobalt delivery devices are delivered to the desired target cells or tissues in vivo, and the bioactive agents are converted from an inactive to an active form upon cellular delivery and cleavage from the organocobalt complex. Since the specification fails to provide particular guidance for target cell delivery and bioactive agent activation upon cleavage from the organocobalt complex in vivo, and since determination of these factors is highly unpredictable, it would require undue experimentation to practice the invention over the scope claimed.

Conclusion

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone numbers for the Group are (703) 308-4242 and (703) 305-3014. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is **(703) 306-5820.** If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, can be reached on (703) 308-0447. Any inquiry regarding this application should be directed to the patent analyst, Katrina Turner, whose telephone number is (703) 305-3413. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Karen A Lacourciere

KAREN LACOURCIERE
PATENT EXAMINER

JZ

June 25, 2003